

Signal Detection Report: Ginkgo biloba for cognitive impairment and dementia

Signal Detection Report date

July, 2017

Key Findings

- Expert opinion: One expert stated that the conclusions of the original review were no longer valid, and was aware of new evidence to strengthen the findings. A second expert stated that the conclusions of the original review were still valid.
- Literature evidence: Qualitative signals (important changes in effectiveness short of “opposing findings”) and one quantitative signal (change in effect size of at least 50%) were generated.

Summary Decision: The original review requires updating

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Introduction

Previous research evaluating a cohort of published systematic reviews demonstrated that 7% of reviews were out of date by the time of publication, while as many as 23% went out of date within two years of being completed[1]. The utility of systematic review-based evidence depends on their remaining up-to-date. As such, the Cochrane Complementary Medicine Field and the Knowledge Synthesis group at the Ottawa Hospital Research Institute (OHRI) have determined a set of existing reviews of interest for which signal detection work using the Ottawa Method's qualitative/quantitative signal detection approach has been performed[1].

The Ottawa method involves identification of qualitative and quantitative signals/triggers indicating the need of updating of a systematic review. [1]. The Ottawa method has been used to assess the need for updating systematic reviews in the past. [1; 2] A graphical overview of our approach and application of the Ottawa signal detection method is provided in Appendix A of this report. This work assessed potential triggers signifying the need for updating of six past Cochrane Complementary Medicine reviews. The conclusion as to whether or not each of the reviews is in need of updating was made based on the identification of qualitative and quantitative signals.

Methods

We contacted content experts to provide input on whether conclusions from the review were still valid, and if they were aware of any new evidence that could potentially signal the need for a review update. This process included the authors from the original review, and also reached out to the lead authors on the included studies of the review. If we did not find sufficient number of experts we then reached out to those who had responded and asked whether they could suggest possible content experts.

Summaries and conclusions were collected for each key question (or possibly key endpoint) within each review; this summary was shared with consulting experts when seeking their input regarding the findings, as well as when establishing the presence of updating triggers. See Appendix B for the survey sent to content experts.

Experts were asked their perspectives on the following features of each review: a) whether the conclusion is still valid in their own opinion (to be answered as yes/no/don't know); b) whether he/she is aware of new evidence published since the publication date of the review being assessed (with details if yes); and c) any additional information or perspectives to be shared. If an expert indicated an opinion that one or more conclusions of the review was out of date and/or provided specific evidence they felt was critical to the decision regarding updating, we verified it by assessing the evidence brought forward by the expert(s).

Experts were given 10 business days to respond. Two reminders were sent, and a conflict of interest disclosure statement was also sent to all experts that participated. The survey was kept open until a minimum of two clinical experts responded.

One reviewer screened the evidence provided by the content experts, and determined whether the studies met the inclusion criteria of the original review. Data was extracted by one reviewer. The identification of qualitative signals was carried out using the Ottawa method qualitative signals. The definition and categories of qualitative signals are presented in Appendix C.

An information specialist provided modified PRESS [13] evaluations of the original review's search strategy, commenting on databases, search dates and terminology. This information is provided in Appendix D in order to inform any future updating for the original review.

Expert Opinion

Of the 6 experts contacted, two responded to our questions on ginkgo biloba for cognitive impairment and dementia. One expert thought that the original review's conclusions were no longer valid, and wrote that "to answer the question whether a specific drug may benefit a patient with a specified disorder, there must be separate meta-analyses for the different Ginkgo products and disorders addressed."

The other expert answered that he believed the conclusions in the original review were still valid, and referenced a large randomized controlled trial that showed no significant difference between Ginkgo and placebo for reducing the incidence of dementia in the elderly with normal cognition or mild cognitive impairment.

Flow

Thirteen references were put forth by the content experts. Nine publications met the original review's inclusion criteria, and were assessed for qualitative signals. One publication was already included in the original review. One publication included patients with no cognitive impairment and was excluded, and two full-texts could not be located.

Signal Detection Results:

Findings of the original review

Overall Conclusion of the Review: "Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable." [3]

Further Details: "36 trials were included but most were small and of duration less than three months. Nine trials were of six months duration (2016 patients). These longer trials were the more recent trials and generally were of adequate size, and conducted to a reasonable standard. Most trials tested the same standardised preparation of Ginkgo biloba, EGb 761, at different doses, which are classified as high or low. The results from the more recent trials showed inconsistent results for cognition, activities of

daily living, mood, depression and carer burden. Of the four most recent trials to report results, three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba. There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing adverse events. A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from nine trials) also showed no consistent pattern of any benefit associated with Ginkgo biloba." [3]

New findings:

Von Gunten et al., 2016 conducted a systematic review of RCTs assessing the effects Ginkgo biloba extract EGb761 versus placebo in patients with the diagnosis of Alzheimer's, vascular dementia or mixed dementia. Studies were only included if they were at least 22 weeks in duration and were of high methodological quality. The authors reported that "four published trials were identified, involving altogether 1,628 outpatients with mild to moderate dementia. Least-square mean differences for change from baseline in cognition, BPSD (including caregiver distress rating), activities of daily living, clinical global impression, and quality of life favoured EGb 761 ($p < 0.001$ for all comparisons)." The authors concluded that "the pooled analyses provide evidence of efficacy of EGb 761 at a daily dose of 240 mg in the treatment of out-patients suffering from Alzheimer's, vascular or mixed dementia with BPSD." [4]

Gauthier and Schlaefke, 2014 performed a systematic review of RCTs assessing the effects of Ginkgo biloba extract EGb761 versus placebo in patients with Alzheimer's, vascular dementia or mixed dementia. Studies were only included if they were at least 20 weeks in duration. Seven RCTs were included with patients treated with 120 mg or 240 mg per day or placebo. The authors reported that "standardized mean differences for change in cognition (-0.52; 95% confidence interval [CI] -0.98, -0.05; $P=0.03$), activities of daily living (-0.44; 95% CI -0.68, -0.19; $P=0.003$), and caregiver distress rating (-0.10; 95% CI -0.92, -0.12; $P=0.01$) significantly favored EGb 761 compared with placebo. Statistically significant superiority of EGb 761 over placebo was confirmed by responder analyses as well as for patients suffering from dementia with neuropsychiatric symptoms." The authors concluded that "meta-analyses confirmed the efficacy and good tolerability of Ginkgo biloba extract EGb 761 in patients with dementia." [5]

Gavrilova et al., 2014 described a RCT of 160 patients with mild cognitive impairment (MCI) who were randomized to receive 240 mg EGb761 daily or placebo for 24 weeks. The authors report that "The Neuropsychiatric Inventory (NPI) composite score decreased by 7.0 ± 4.5 (mean, standard deviation) points in the EGb 761-treated group and by 5.5 ± 5.2 in the placebo group ($p=0.001$). Improvement by at least 4 points was found in 78.8% of patients treated with EGb 761 and in 55.7% of those receiving placebo ($p=0.002$). Superiority of EGb 761 over placebo ($p<0.05$) was also found for the State-Trait Anxiety Inventory score, the informants' global impression of change, and both Trail-Making Test scores. There were statistical trends favoring EGb 761 in the Geriatric Depression Scale and the patients' global impression of change." The authors conclude that "EGb 761 improved NPI and cognitive performance in patients with MCI. The drug was safe and well tolerated." [6]

Herrschaft et al., 2012 described a RCT of 410 patients with mild to moderate dementia (Alzheimer's or vascular dementia) and randomized to receive 240 mg Gingko biloba extract EGb761 daily or placebo for 24 weeks. The authors reported that "Patients treated with EGb 761 (n = 200) improved by 2.2 ± 3.5 points (mean \pm sd) on the Short Cognitive Performance Test (SKT) total score, whereas those receiving placebo (n = 202) changed only slightly by 0.3 ± 3.7 points. The NPI composite score improved by 4.6 ± 7.1 in the EGb 761-treated group and by 2.1 ± 6.5 in the placebo group. Both drug-placebo comparisons were significant at $p < 0.001$. Patients treated with EGb 761 also showed a more favourable course in most of the secondary efficacy variables." The authors conclude that "treatment with EGb 761_ at a once-daily dose of 240 mg was safe and resulted in a significant and clinically relevant improvement in cognition, psychopathology, functional measures and quality of life of patients and caregivers." [7]

Nacu and Hoerr, 2016 reported a secondary descriptive analysis of Herrschaft et al., 2012 with no additional data. [8]

Ihl et al., 2011 is the main study for its two companion studies reported below. Bachinskaya et al., 2011 focuses only on Neuropsychiatric Inventory (NPI) outcome and provides detailed data on various items of NPI, while the main study reports on various outcomes and only mentions NPI total score with no further details. Ihl et al., 2012 reports separate data for two subgroups (Alzheimer's versus vascular dementia,) while the main study provides overall results.) Ihl et al., 2011 describes a RCT of 410 patients with mild to moderate dementia (Alzheimer's, vascular dementia or mixed form), randomized to receive 240 mg of Gingko biloba EGb 761 or placebo once daily for 12 weeks. The authors report that "patients treated with EGb 761 (n=202) improved by -1.4 (95% confidence interval (-1.8; -1.0)) points on the SKT and by -0.2 (-4.0; -2.3) on the NPI total score, whereas those receiving placebo (n=202) deteriorated by +0.3 (-0.1; 0.7) on the SKT and had a change of 0 on the NPI total score (-0.9; 0.9). Both drug-placebo comparisons were statistically significant at $p < 0.001$. EGb 761 was significantly superior to placebo with respect to all secondary outcome measures." The authors conclude that "EGb 761, 240 mg once-daily, was found significantly superior to placebo in the treatment of patients with dementia with neuropsychiatric symptoms." [10]

Ihl et al., 2012, a companion study for Ihl et al., 2012, described a RCT that included 333 patients with mild or moderate dementia (diagnosed with Alzheimer's or vascular dementia), randomized to receive 240 mg of Gingko biloba EGb 761 once daily for 24 weeks. The authors report that "EGb 761[®] treatment was superior to placebo with respect to the SKT total score (drug-placebo differences: 1.7 for AD, $p < 0.001$, and 1.4 for VaD, $p < 0.05$) and the NPI total score (drug-placebo differences: 3.1 for AD, $p < 0.001$ and 3.2 for VaD, $p < 0.05$). Significant drug-placebo differences were found for most secondary outcome variables with no major differences between AD and VaD subgroups." The authors concluded that "EGb 761 improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia." [9]

Bachinskaya et al., 2011 is also a companion study to Ihl et al., 2011 that included 410 patients with mild to moderate dementia (Alzheimer's or vascular dementia) and randomized to receive 240 mg Gingko biloba extract EGb761 daily or placebo for 24 weeks. The authors reported that "the NPI composite score improved by -3.2 (95% confidence interval -4.0 to -2.3) in patients taking EGb 761 (n =

202), but did not change (-0.9; 0.9) in those receiving placebo (n = 202), which resulted in a statistically significant difference in favor of EGb 761® (P < 0.001). Treatment with EGb 761 was significantly superior to placebo for the symptoms apathy/indifference, sleep/night-time behavior, irritability/lability, depression/dysphoria, and aberrant motor behavior. The authors conclude that “treatment with EGb 761®, at a once-daily dose of 240 mg, was safe, effectively alleviated behavioral and neuropsychiatric symptoms in patients with mild to moderate dementia.” [11]

Napryeyenko et al., 2009 reports a secondary analysis of Napryeyenko et al., a 2005 RCT in which 395 patients diagnosed with dementia with neuropsychiatric features were included. This publication reports the results broken down by Alzheimer’s disease (AD) and vascular dementia (VaD). Patients were randomly allocated to receive 240 mg Ginkgo biloba EGb 761 or placebo for 22 weeks. The authors report that “under EGb 761® treatment the SKT total score improved by -3.0±2.3 and -3.4±2.3 points in patients with AD and VaD respectively, whereas the patients on placebo deteriorated by +1.2±2.5 and +1.5±2.2 points, respectively (p=0.01 for both drug-placebo differences). Significant drug-placebo differences were found for all secondary outcome variables with no major differences between AD and VaD subgroups.” The authors concluded that “the subgroup analyses demonstrated that the Ginkgo biloba extract EGb 761® was safe and effective in the treatment of both major types of dementia, AD and VaD. This may be an advantage in the management of patients with mixed pathologies, when none of the two diagnoses can readily be established, in particular in a primary care setting.” [12]

Adverse effects:

No safety alerts were identified for Ginkgo biloba EGb 761 in the United States, Canada or the United Kingdom. All new evidence reported similar rates of adverse events between treatment and placebo groups. Several studies reported a higher rate of adverse events for the placebo group with regards to dizziness (Napryeyenko, Bachniskaya, Herrschaft).

Qualitative Signal: Signals detected (Important changes in effectiveness short of “opposing findings”)

All new evidence put forth by the content experts had higher doses of Ginkgo biloba (240 mg per day) and longer treatment periods (22 - 26 weeks) than the original review. Sample size in the RCTs ranged from 160 – 410 patients, and the systematic reviews included totals of 1,628[4] and 2,684[5] patients.

Patient groups were also similar across the majority of new studies, including those with Alzheimer’s disease or vascular dementia (except Grass-kapenke and Garilova, which included patients with mild cognitive impairment). There was trial overlap in the systematic reviews, which both included Napryeyenko 2007 (secondary analysis 2009), Ihl 2011, and Herrschaft 2012.

All new studies found evidence of efficacy of EGb 761 in the treatment of patients suffering from AD, VaD or mild cognitive impairment.

New findings consistently favored Ginkgo biloba compared to placebo for the reported outcomes of interest [Global (CGIC), Cognition (SKT), mood, and activities of daily living] for ≥ 22 weeks duration and ≥ 200 mg daily dose (see quantitative signals section below for detail.) New pooled estimates are based on larger sample size (at least twice the sample size included in the original review for each of the outcomes) and they consistently demonstrated benefit of Ginkgo biloba versus placebo. Given that the new findings strengthen and confirm the original review's findings for the stated outcomes, we consider them as signals (Important changes in effectiveness short of "opposing findings").

Quantitative Signal: One signal detected

Clinical Global Improvement of Change (CGIC) (numbers improved or unchanged compared with baseline) after treatment of 24-26 weeks (Ginkgo biloba dose greater than 200mg/day), meta-analysis # 1.7.2: After adding data from two new primary studies [6, 10], the new pooled estimate (Figure 1, Appendix E) remained statistically significant favoring the intervention (OR 2.00, 95% CI 1.46, 2.72; N=779 versus original review OR 1.80, 95% CI 1.22, 2.65; N=549).

Herrschaft 2012 [7] reported continuous data for this outcome that we could not add to the above meta-analysis. However, von Gunten 2016 [4] reported pooled SMD including both ADCS-CGIC and GBS scales favoring treatment (SMD -0.75, 95% CI -0.85, -0.65). It is important to note that the original review has focused on each scale separately for this outcome.

Cognition, SKT (change from baseline after treatment of 22-26 weeks) for Ginkgo biloba dose greater than 200mg/day, meta-analysis # 1.13.2: Data from four new primary studies reported in von Gunten 2016 [4] were added in the meta-analysis and the new pooled estimate remained statistically significant favoring Ginkgo biloba [new pooled MD -2.93, 95% CI -3.17, -2.70 (N=2281) versus original review MD -3.54, 95% CI -3.94, -3.14 (N=683)] with change in magnitude (Figure 2a and 2b, Appendix E).

Mood and emotional function (NPI-12) (change from baseline after treatment of 22 weeks), meta analysis #1. 20.2: von Gunten 2016 [4] reported a pooled estimate originating from four studies for 22-24 weeks (SMD -3.65, 95% CI -4.50, -3.21). We could not add the reported estimate from one study in the original review in this meta-analysis as it was reported in a different format (treatment effect -7.10, SE 0.43, 95% CI -7.94, -6.26 with no per arm data). The meta-analyses (N= 1598) demonstrated consistent significant results to the original review estimate. We could not pool the data reported by Herrschaft et al., 2012 with the evidence in the original review due to different reporting format (mean and 95% CI in Herrschaft et al., 2012: -4.6 (-5.6, -3.6) in treatment arm, and -2.1 (-3.0, -1.2) in control group versus treatment effect -7.10, SE 0.43, 95% CI -7.94, -6.26 in the original review MA#1.20.2 with no per arm data).

The new evidence consistently favoured the intervention: "The NPI composite score improved by 4.6 ± 7.1 in the EGb 761-treated group and by 2.1 ± 6.5 in the placebo group. Both drug-placebo comparisons were significant at $p < 0.001$." [4] Similarly, Ihl 2012 favored the intervention (change from baseline) for NPI total score: mean -4.5 95% CI -6.6, -2.3 in intervention versus mean -1.3, 95% CI -3.4, +0.9 in the

placebo group, p-value: 0.036.[9] Bachinskaya et al., 2011, the companion paper to Ihl et al. 2012, reported that “the NPI composite score improved by -3.2 (95% CI -4.0 to -2.3) in patients taking EGb 761 (n = 202), but did not change (95% CI -0.9; 0.9) in those receiving placebo (n = 202), which resulted in a statistically significant difference in favor of EGb 761® (P < 0.001).”[11] Napryeyenko et al., 2009 also demonstrated benefit of the intervention (mean (SD): -7.0 (5.1) in intervention versus 2.8(6.1), p-value<0.01 in placebo arms.)[12]

Activities of daily living (change from baseline after treatment of 22-24 weeks), meta-analysis #1.18.2: New evidence from three primary studies that were reported in a meta-analysis by Gauthier et al., 2014 [5] was added to the meta-analysis in the original review. The new pooled estimate (Figure 3, Appendix E) remained statistically significant favoring the intervention with minimal change in magnitude (new pooled SMD -0.40, 95% CI -0.48, -0.31; N=2230 versus original review SMD -0.43, 95% CI -0.56, -0.30; N=1027).

Number of patients experiencing an adverse event during treatment of 24-26 weeks (Ginkgo biloba dose greater than 200mg/day): New evidence from four primary studies that were reported in a meta-analysis by Gauthier et al., 2014 [4] were added to the meta-analysis in the original review. Similar to the original review findings, the new pooled estimate (Figure 4, Appendix E) demonstrated non statistically significant results (new pooled OR 0.94, 95% CI 0.79, 1.13 versus OR 0.71, 95% CI 0.49, 1.01).

Number of patients experiencing a serious adverse event during treatment of 24 weeks (Ginkgo biloba dose greater than 200mg/day), meta-analysis # 1. 28.2: New evidence from four primary studies that were reported in a meta-analysis by Gauthier et al., 2014 [4] were added to the meta-analysis in the original review. Consistent to the original review findings, the new pooled estimate (Figure 5, Appendix E) demonstrated non statistically significant results (new pooled OR 0.89, 95% CI 0.55, 1.45 versus OR 0.67, 95% CI 0.36, 1.27)..

Cognition, SKT(change from baseline after treatment of 22-26 weeks) for Ginkgo biloba dose greater than 200mg/day for AD subgroup: Data from one new primary study [12] was added to the analysis and the pooled estimate consistently remained statistically significant favoring Ginkgo biloba [pooled MD - 3.34, 95% CI -3.88, -2.80 (N=372, 2 studies) versus original review MD -1.30, 95% CI -2.29, -0.31 (N=158, one study)] with change in magnitude (Figure 6, Appendix E). The pooled estimate met the quantitative signal criteria for change in effect size of at least 50% (One Signal). However, this pooled estimate is based on only two studies with a high degree of heterogeneity ($I^2=96\%$). As such, it may or may not affect conclusions for this outcome. Ihl et al., 2012 reported SKT total score Mean -1.4, 95%CI -1.9, -1.0.

Conclusion: The new evidence consistently favors the intervention and is confirmatory to the findings of the original review for the stated specific outcomes. Qualitative signals (important changes in effectiveness short of “opposing findings), and one quantitative signal (change in effect size of at least 50%) were generated. This may have the potential to change the conclusion for some parts of the original review.

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Appendix A: Overview of the Modified Ottawa Method

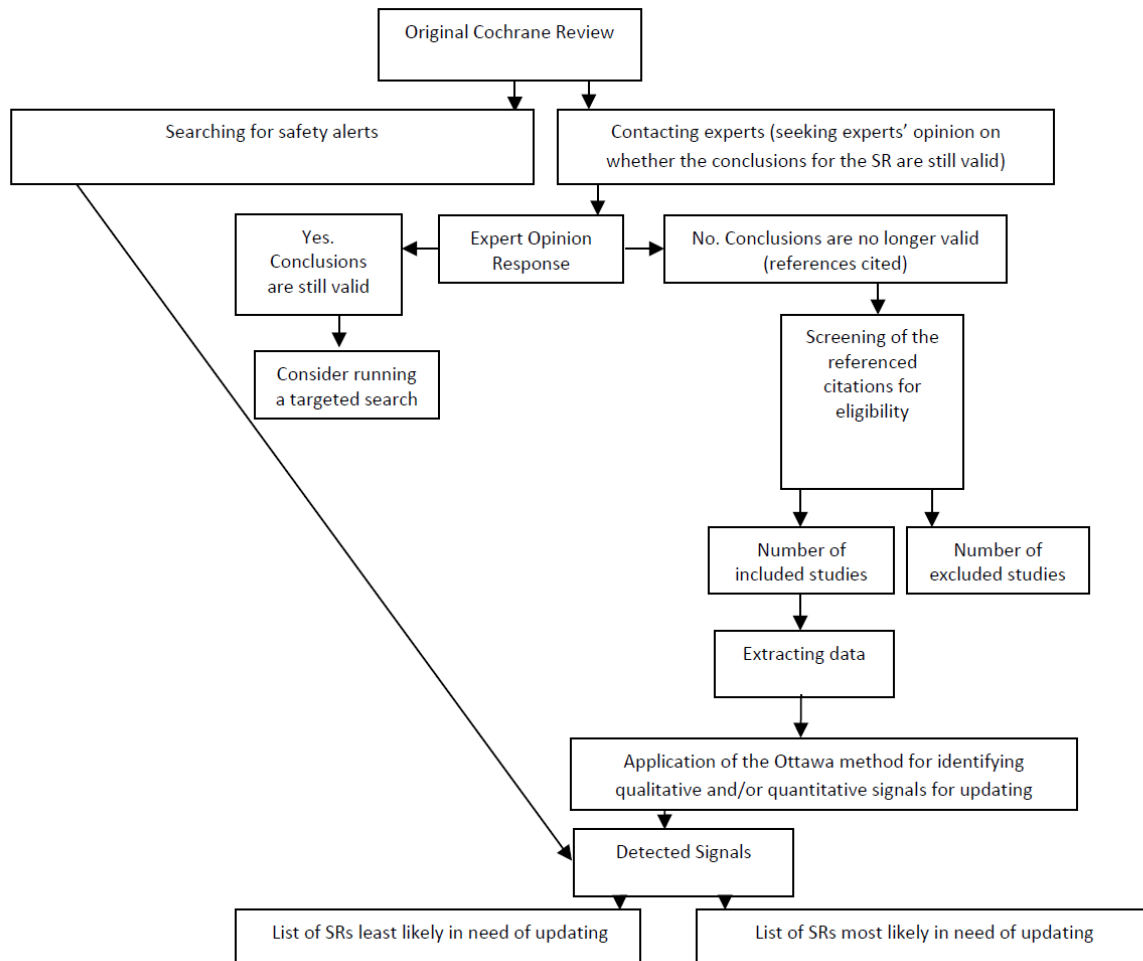


Figure 1: The process of signal detection methods for Cochrane reviews

Appendix B: Expert Opinion Survey

Conclusions from systematic review	Is the conclusion(s) in this review still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in this review? (Yes/No/Don't know) If yes, please provide references	Comments
<p>Review Objective: To assess the efficacy and safety of Ginkgo biloba (oral or intravenous, any doses) for the treatment of people with dementia or cognitive decline.</p>			
<p>Overall Conclusion of the Review: Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.</p> <p><u>Further Details:</u> 36 trials were included but most were small and of duration less than three months. Nine trials were of six months duration (2016 patients). These longer trials were the more recent trials and generally were of adequate size, and conducted to a reasonable standard. Most trials tested the same standardised preparation of Ginkgo biloba, EGb 761, at different doses, which are classified as high or low. The results from the more recent trials showed inconsistent results for cognition, activities of daily living, mood, depression and carer burden. Of the four most recent trials to report results three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba. There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing adverse events. A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from nine trials) also</p>			

<p>showed no consistent pattern of any benefit associated with Ginkgo biloba.</p>			
<p>Global Function: The CGIC scale, measuring clinical global improvement as assessed by the physician (Schneider 1997), was dichotomized between participants who showed improvement or were unchanged and those who were worse. There is benefit associated with Ginkgo biloba (dose greater than 200 mg/day) at 24 weeks (207/276 compared with 178/273, OR 1.66, 95% CI 1.12 to 2.46, P = 0.01) (2 studies), but not for the lower dose. Two studies used the SCAG (Shader 1974), an 18-item scale that assesses global function. There is benefit associated with Ginkgo biloba (dose less than 200 mg/day) compared with placebo at less than 12 weeks (MD -14.70, 95% CI -28.0 to -1.4, P = 0.03, one study), and at 12 weeks (MD -22.20, 95% CI -29.4 to -15.0, P < 0.00001, one study). Le Bars 1997 found a significant difference between treatment and control groups in GERRI scores but not in CGIC.</p>			
<p>Cognitive Function: <u><12 weeks:</u> The meta-analysis of cognition included data from 4 trials using 4 different tests: Expanded Mental Control Test (EMCT) (Brautigam 1998,) speed of learning test (Graessel 1992,) Vienna Reaction test Mancini 1993 (Hofferberth 1989,) and Toulouse-Pieron Cancellation Test (Mancini 1993.) There is significant heterogeneity between the trials (I2= 92.1%). There is no significant difference between Ginkgo biloba and placebo. The removal of Hofferberth 1989 from the meta-analysis reduces the measure of heterogeneity (I2 = 0%). Hofferberth 1989 has a significant treatment effect but the other three trials do not. <u>>12weeks:</u> The meta-analysis of data at 12 weeks included 5 trials. Graessel 1992, speed of learning test Maurer 1997, the SKT Vorberg 1989, Crichton memory impairment sub-test Weitbrecht 1985, Wechslet digit symbol Wesnes 1987, Benton digit span. There is significant heterogeneity between the trials (I2 = 76.6%). There is a significant difference between Ginkgo biloba and placebo in favour of Ginkgo</p>			

<p>biloba (SMD -0.65, 95% CI -1.22 to -0.09, P = 0.02). The treatment effect is very variable. The removal of the trial with the largest treatment effect (Vorberg 1989) reduces the measure of heterogeneity (I² = 46.5%)</p> <p>ADAS-cog: Three trials used the ADAS-Cog DIGGER 2008, Schneider 2005 and Le Bars 1997. There was no significant difference between Ginkgo biloba and placebo for low or high dose. There was significant heterogeneity between the trials (I² = 65.5%).</p> <p>SKT: Four trials used the SKT, Mazza 2006, Napryeyenko 2005, Kanowski 1996, and Van Dongen 2000. There was significant heterogeneity between the trials (I² = 97%). There was significant difference in favour of Ginkgo biloba for the low and high dose, and all doses pooled. (MD -3.07, 95% CI -3.96 to -2.17, P < 0.00001, 2 studies) (MD -3.54, 95% CI -3.94 to -3.14, P < 0.00001, 3 studies) (MD -3.57, 95% CI -3.94 to -3.20, P < 0.00001, 4 studies). A sensitivity analysis was carried out, analysing each pair of trials separately. For all doses of Ginkgo biloba, there is no significant difference between placebo and Ginkgo biloba for a pooled analysis of Van Dongen 2000 and Kanowski 1996, but there is significant heterogeneity between these two trials (I² = 64%). The results of Mazza 2006 and Napryeyenko 2005 are very similar, and there is a significant effect of Ginkgo biloba (MD -4.47, 95% CI -4.89 to -4.04).</p> <p>EMCT: One trial, Brautigam 1998, used the EMCT. There was no significant difference between Ginkgo biloba (low dose) and placebo</p>			
<p>Activities of Daily Living:</p> <p>The result from one study using the Crichton Rating Scale (CRS Robinson 1964) shows benefit for Ginkgo biloba (dose less than 200 mg/day) compared with placebo at 12 weeks (MD -5.0, 95% CI -7.88, -2.12, P = 0.0007, one study), but not at 22-26 weeks using the GERRI and NAI-NAA, at 24 weeks, and for the higher dose at 24 weeks (SMD -0.43, 95% CI -0.55 to -0.30, P < 0.00001, 4 studies) and for all doses pooled (SMD -0.36, 95% CI -0.46 to -0.25, P < 0.00001, 5 studies). There is significant heterogeneity within the higher dose studies (I² ></p>			

<p>90%) which was reduced to 0% by removing Napryeyenko 2005 from the analysis and then the results show no significant difference between Ginkgo biloba and placebo for the high dose and for all doses pooled.</p>			
<p><u>Mood and Emotional Function:</u> One study used the ADAS-Noncog (Rosen 1984), which assesses function over several domains not including cognitive function. There was no difference between Ginkgo biloba, high dose, at 12 weeks and placebo. Napryeyenko 2005 and DIGGER 2008 used the NPI-12 and there was a significant difference in favour of Ginkgo biloba (MD -7.10, 95% CI -7.95 to -6.25, P < 0.00001) for the higher dose but not for the lower dose. Napryeyenko 2005 assessed depression using the Hamilton Depression Scale and found a significant difference in favour of Ginkgo biloba higher dose (MD -5.30, 95% CI -6.07 to -4.53, P < 0.00001).</p>			
<p><u>Quality of Life:</u> Quality of life, patient and carer rated was assessed in the DIGGER 2008 study, using three different measures. There were no significant differences between Ginkgo biloba and placebo.</p>			
<p><u>Adverse Events:</u> There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing any adverse events. There were significant differences, in favour of high dose Ginkgo biloba compared with placebo for three causes of adverse events, dizziness, tinnitus, headache, angina pectoris and increased blood pressure. The two studies were Napryeyenko 2005 and Schneider 2005, the single study Napryeyenko 2005. dizziness (23/370 compared with 48/374) (OR 0.45 95% CI 0.27 to 0.75, P = 0.002) (2 studies) tinnitus (16/370 compared with 30/374) (OR 0.52 95% CI 0.28 to 0.97, P = 0.04) (2 studies) headache (56/370 compared with 94/374) (OR 0.48 95% CI 0.32 to 0.71, P = 0.0002) (2 studies) angina pectoris (20/200 compared with 35/200) (OR 0.52 95% CI 0.29 to 0.94, P = 0.03) (1 study) increased blood pressure (4/200 compared with 13/200) (OR</p>			

0.29 95% CI 0.09 to 0.92, P = 0.03) (1 study).			
<p>Subgroup Analyses for only those patients with Alzheimer’s Disease:</p> <p>Global Functioning: The CGIC scale, measuring clinical global improvement as assessed by the physician (Schneider 1997), was dichotomized between participants who showed improvement or were unchanged and those who were worse. There are benefits associated with Ginkgo biloba (dose greater than 200 mg/day) at 24 weeks (181/ 249 compared with 154/253, OR 1.79, 95% CI 1.21 to 2.65, P = 0.003) (2 studies), but not for the lower dose.</p> <p>ADAS-Cog: Two trials used the ADAS-Cog, Le Bars 1997 and Schneider 2005. There was no significant difference between Ginkgo biloba and placebo for low or high dose.</p> <p>SKT: Two trials used the SKT, Mazza 2006 and Kanowski 1996. There was significant difference in favour of Ginkgo biloba for the low dose (MD -4.30, 95% CI -5.34 to -3.26, P < 0.00001) (1 study) and high dose (MD -1.30, 95% CI -2.29 to -0.31, P = 0.01) (1 study).</p> <p>Activities of Daily Living: Schneider 2005 and Le Bars 1997 used the Geriatric Evaluation by Relative’s Rating Instrument (GERRI) which includes cognitive, social and mood items assessed by a carer, and Kanowski 1996 used the NAI-NAB which assesses the degree of independence by means of the patient’s ability to cope with everyday tasks. There was no significant difference between Ginkgo biloba and placebo for low or high dose.</p> <p>Adverse Events: There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing any adverse events.</p>			
<p>Varying doses of Ginkgo:</p> <p>There is considerable heterogeneity between the trials for both lower dose and higher dose of Ginkgo biloba, which is much reduced when Mazza 2006 and Napryeyenko 2005 are omitted. There is no benefit of Ginkgo biloba at the lower dose with and without Mazza 2006, and at the higher dose a</p>			

<p>significant benefit of Ginkgo biloba (SMD -0.64, 95% CI -0.77 to -0.51, P < 0.0001, I2 = 98%) is reduced (SMD -0.07, 95% CI -0.23 to 0.09, P = 0.40, I2 = 65%) and there is no significant difference between Ginkgo biloba and placebo.</p>			
<p>Abbreviations: ADAS-Cog (Alzheimer's Disease Assessment Scale –cognition); CGIC (Clinical Global Impression of Change); EMCT (Expanded Memory Control Test); GERRI (Geriatric Evaluation by Relative's Rating Scale); SCAG (Sandoz Clinical Assessment - Geriatric Scale); SKT (Syndrom Kurz Test); MD (mean difference)</p>			

Appendix C: The Ottawa Method Qualitative Signals*

Potentially invalidating change in evidence

This refers to a situation in which it is expected that clinicians do not act upon the results of the original systematic review (SR) and the agency/organization that supported the original production of the SR would retract the SR until it is updated. Criteria for potentially invalidating change in evidence are presented below.

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix D: Modified PRESS Review for Original Review's Search Strategy

The original search was executed on September 20, 2007 in the specialized register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG). Additional searches were performed in multiple databases on January 3, 2008 to incorporate records not covered by the dates in the register. Readers are directed to the Group's Module in The Cochrane Library for a list of terms searched for the CDCIG. The ginkgo biloba search terms specific to the review are listed in the methods section but do not appear in an appendix, although it is possible the full strategies are available on request.

There appear to be additional synonyms for ginkgo biloba, including ginko, ginkyo, salisburia, and other terms such as fossil or maidenhair tree, that may have increased the reach of the original searches. Without seeing the exact strategies as run in each database, complete with full database name and version, fields searched, date run and number of hits per line, it is difficult to fully assess the quality of the searches. However, the search strategies designed for the various Cochrane review groups are designed for sensitivity and as such should well address the population group pertinent to this review, exclusive of the ginkgo biloba intervention.

In conclusion, the strategy has some potential limitations with regard to vocabulary. The greatest limitation is with regard to the availability of the searches as executed and the inclusion of at least one of the database searches in an appendix.

Appendix E: Meta-analyses (Figures 1-6)

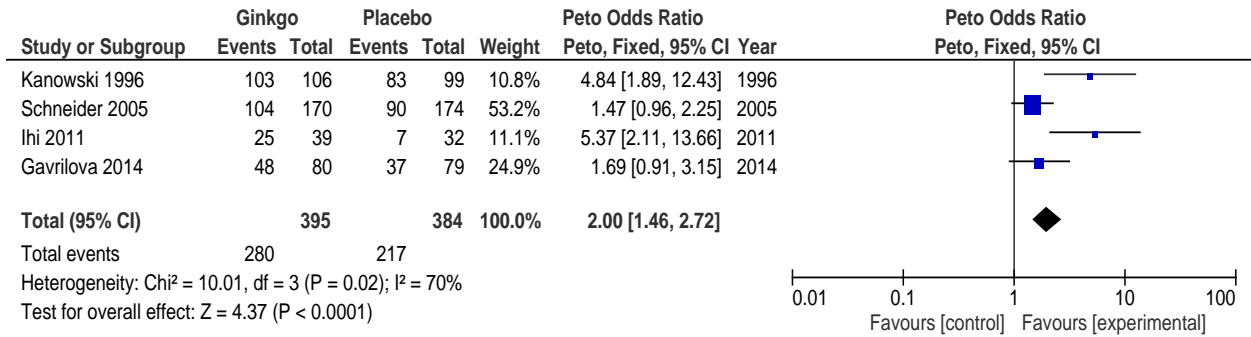


Figure 1: Global XXX (CGIC) (numbers improved or unchanged compared with baseline) after treatment of 24-26 weeks (Ginkgo biloba dose greater than 200mg/day)

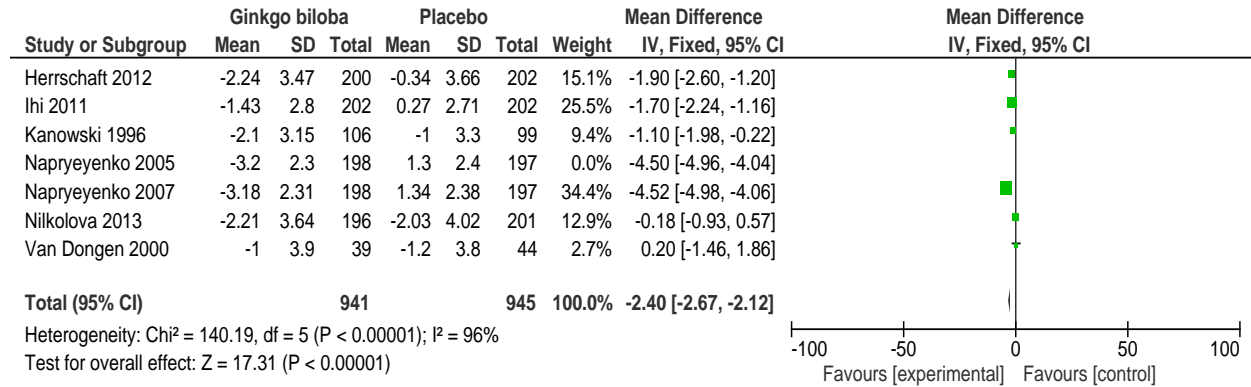


Figure 2a: Cognition, SKT(change from baseline after treatment of 22-26 weeks) for Ginkgo biloba dose greater than 200mg/day (excluding Napryeyenko 2005)

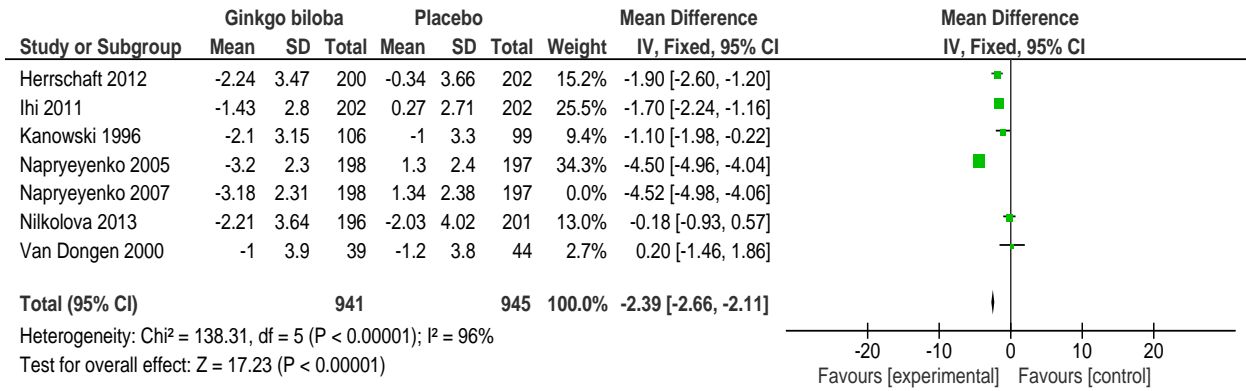


Figure 2b: Cognition, SKT(change from baseline after treatment of 22-26 weeks) for Ginkgo biloba dose greater than 200mg/day (excluding Napryeynko 2007)

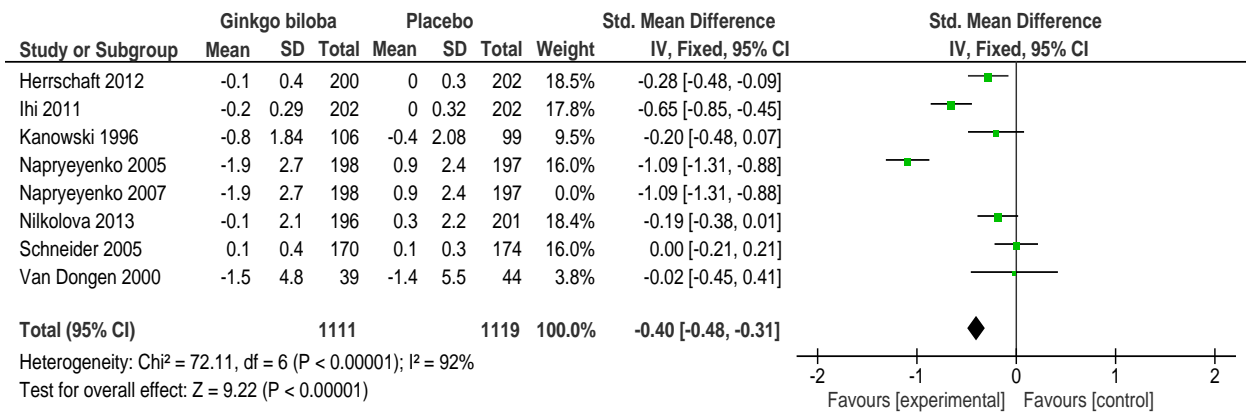


Figure 3: Activities of Daily Living (change from baseline after treatment of 22-24 weeks)

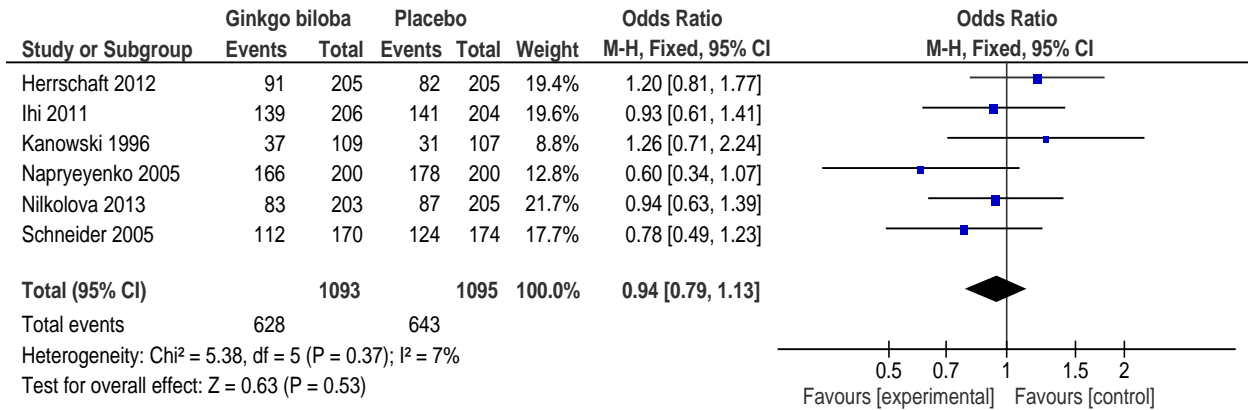


Figure 4: Number of patients experiencing an adverse event during treatment of 24-26 weeks (Ginkgo biloba dose greater than 200mg/day)

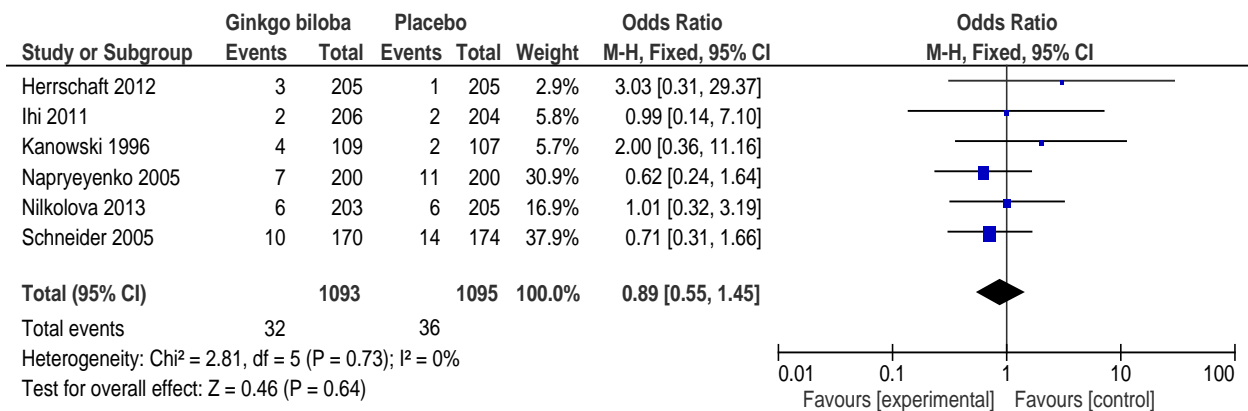


Figure 5: Number of patients experiencing a serious adverse event during treatment of 24 weeks (Ginkgo biloba dose greater than 200mg/day)

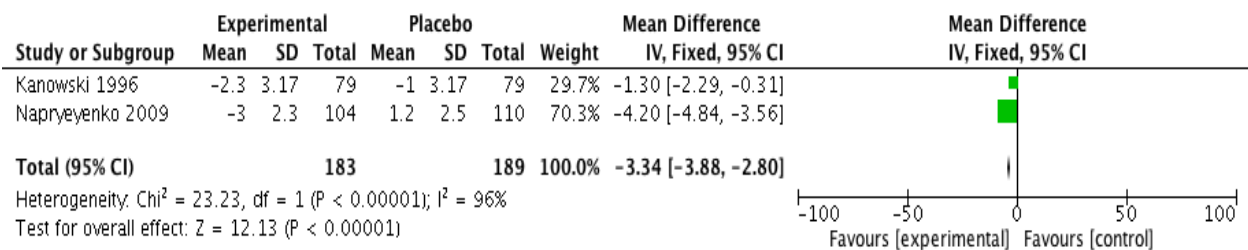


Figure 6: Cognition, SKT (change from baseline after treatment of 22-26 weeks) for Ginkgo biloba dose greater than 200mg/day for AD subgroup